Figure 1

```
GAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTC      50
GGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTA     100
TCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGG     150
ATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGGGCAG     200
AGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTACATGGAGCTGA     250
GCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGCGCCA     300
TTACGATTTTTGGAGTGGTCCACCCAAGACCACTACTACTACTACTACAT     350
GGACGTCTGGGGCAAAGGGACCACGGTCACCGTCTCAAGC               390
```

Figure 2

EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGG 50
IIPIFGTANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARAP 100
LRFLEWSTQDHYYYYYMDVWGKGTTVTVSS 130

Figure 3

```
ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACTGGAGT      50
ACATTCAGAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTG     100
GGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGC     150
TATGCTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGAT     200
GGGAGGGATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCC     250
AGGGCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTACATG     300
GAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAG     350
AGCGCCATTACGATTTTTGGAGTGGTCCACCCAAGACCACTACTACTACT     400
ACTACATGGACGTCTGGGGCAAAGGGACCACGGTCACCGTCTCAAGCGCC     450
TCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCAC     500
CTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG     550
AACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCAC     600
ACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGT     650
GGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG     700
TGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAA     750
TCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCT     800
GGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCA     850
TGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCAC     900
GAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCA     950
TAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGG    1000
TGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAG    1050
TACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAAC    1100
CATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGC    1150
CCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTG    1200
GTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGG    1250
GCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACG    1300
GCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAG    1350
CAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCA    1400
CTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA              1440
```

Figure 4

MGWSCIILFLVATATGVHSEVQLVQSGAEVKKPGSSVKVSCKASGGTFSS 50
YAISWVRQAPGQGLEWMG**GIIPIFGTANYAQKFQG**RVTITADKSTSTAYM 100
ELSSLRSEDTAVYYCAR**APLRFLEWSTQDHYYYYYMDV**WGKGTTVTVSSA 150
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH 200
TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK 250
SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH 300
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE 350
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL 400
VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ 450
QGNVFSCSVMHEALHNHYTQKSLSLSPGK 479

Figure 5

```
TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGAC      50
AGTCAGGATCACATGCCAAGGAGACAGCCTCAGAAGCTATTATGCAAGCT     100
GGTACCAGCAGAAGCCAGGACAGGCCCCTGTACTTGTCATCTATGGTAAA     150
AACAACCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCAGCTCAGG     200
AAACACAGCTTCCTTGACCATCACTGGGGCTCAGGCGGAAGATGAGGCTG     250
ACTATTACTGTAACTCCCGGGACAACAGTGATAACCGTCTGATATTTGGC     300
GGCGGGACCAAGCTGACCGTCCTCAGT                            327
```

Figure 6

SSELTQDPAVSVALGQTVRITC**QGDSLRSYYAS**WYQQKPGQAPVLVIY**GK** 50
NNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYC**NSRDNSDNRLI**FG 100
GGTKLTVLS 109

Figure 7

ATGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACTGGAGT 50
ACATTCATCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGG 100
GACAGACAGTCAGGATCACATGCCAAGGAGACAGCCTCAGAAGCTATTAT 150
GCAAGCTGGTACCAGCAGAAGCCAGGACAGGCCCCTGTACTTGTCATCTA 200
TGGTAAAAACAACCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCA 250
GCTCAGGAAACACAGCTTCCTTGACCATCACTGGGGCTCAGGCGGAAGAT 300
GAGGCTGACTATTACTGTAACTCCCGGGACAACAGTGATAACCGTCTGAT 350
ATTTGGCGGCGGGACCAAGCTGACCGTCCTCAGT*CAGCCCAAGGCTGCCC* 400
CCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG 450
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT 500
GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCA 550
CACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGC 600
CTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC 650
GCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTGCAGAATGCTCTT 700
GA 702

Figure 8

MGWSCIILFLVATATGVHSSSELTQDPAVSVALGQTVRITC**QGDSLRSYY** 50
ASWYQQKPGQAPVLVIY**GKNNRPS**GIPDRFSGSSSGNTASLTITGAQAED 100
EADYYC**NSRDNSDNRLI**FGGGTKLTVLS*QPKAAPSVTLFPPSSEELQANK* 150
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLS 200
LTPEQWKSHRSYSCQVTHEGSTVEKTVAPAECS 233

Figure 9

```
TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGAC      50
AGTCAGGATCACATGCCAAGGAGACAGCCTCAGAAGCTATTATGCAACCT     100
GGTACCAGCAGAAGCCAGGACAGGCCCCTATTCTTGTCATCTATGGTGAA     150
AATAAGCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCAGCTCAGG     200
AAACACAGCTTCCTTGACCATCACTGGGGCTCAGGCAGAAGATGAGGCTG     250
ACTACTATTGTAAATCTCGGGATGGCAGTGGTCAACATCTGGTGTTCGGC     300
GGAGGGACCAAGCTGACCGTCCTAGGT                            327
```

Figure 10

SSELTQDPAVSVALGQTVRITC**QGDSLRSYYAT**WYQQKPGQAPILVIY**GE** 50
NKRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYC**KSRDGSGQHLV**FG 100
GGTKLTVLG 109

Figure 11

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACTGGAGT 50
ACATTCATCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGG 100
GACAGACAGTCAGGATCACATGCCAAGGAGACAGCCTCAGAAGCTATTAT 150
GCAACCTGGTACCAGCAGAAGCCAGGACAGGCCCCTATTCTTGTCATCTA 200
TGGTGAAAATAAGCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCA 250
GCTCAGGAAACACAGCTTCCTTGACCATCACTGGGGCTCAGGCAGAAGAT 300
GAGGCTGACTACTATTGTAAATCTCGGGATGGCAGTGGTCAACATCTGGT 350
GTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCC 400
CCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG 450
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT 500
GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCA 550
CACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGC 600
CTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC 650
GCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTGCAGAATGCTCTT 700
GA 702

Figure 12

MGWSCIILFLVATATGVHSSSELTQDPAVSVALGQTVRITC**QGDSLRSYY** 50
ATWYQQKPGQAPILVIYGENKRPSGIPDRFSGSSSGNTASLTITGAQAED 100
EADYYC**KSRDGSGQHLV**FGGGTKLTVLG*QPKAAPSVTLFPPSSEELQANK* 150
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLS 200
LTPEQWKSHRSYSCQVTHEGSTVEKTVAPAECS 233

Figure 13

Heavy chain CDR1	CDR2	CDR3	
SYAIS	GIIPIFGTANYAQKFQG	APLRFLEWSTQDHYYYYYMDV	2F8/A12

Light chain CDR1	CDR2	CDR3	
QGDSLRSYYAS	GKNNRPS	NSRDNSDNRLI	2F8
QGDSLRSYYAT	GENKRPS	KSRDGSGQHLV	A12

Figure 14

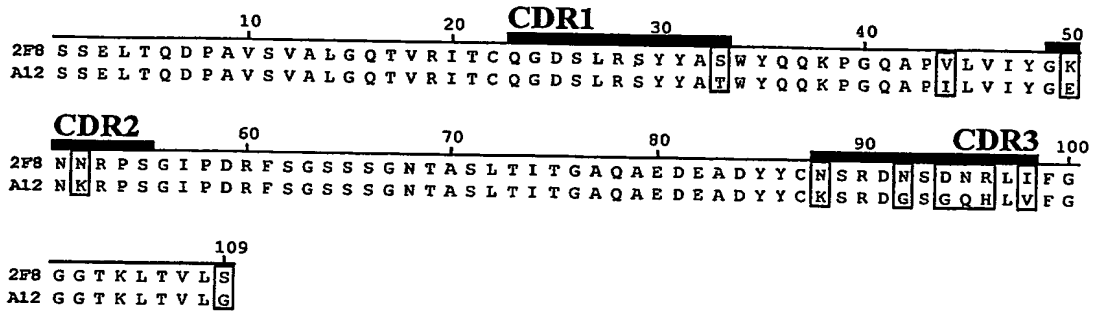

CDR1
CDR2
CDR3
2F8 S S E L T Q D P A V S V A L G Q T V R I T C Q G D S L R S Y Y A S W Y Q Q K P G Q A P V L V I Y G K
A12 S S E L T Q D P A V S V A L G Q T V R I T C Q G D S L R S Y Y A T W Y Q Q K P G Q A P I L V I Y G E
2F8 N N R P S G I P D R F S G S S S G N T A S L T I T G A Q A E D E A D Y Y C N S R D N S D N R L I F G
A12 N K R P S G I P D R F S G S S S G N T A S L T I T G A Q A E D E A D Y Y C K S R D G S G Q H L V F G
2F8 G G T K L T V L S
A12 G G T K L T V L G

Figure 15

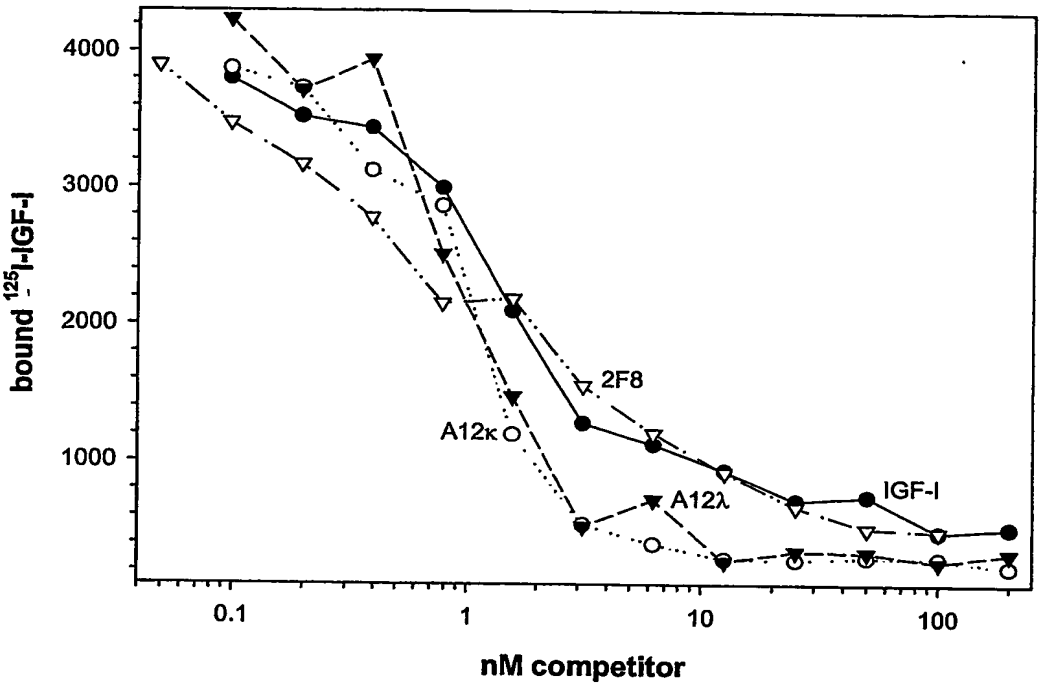

4000
3000
2000
1000
bound ^{125}I-IGF-I
0.1
1
10
100
nM competitor
2F8
A12κ
A12λ
IGF-I

Figure 16

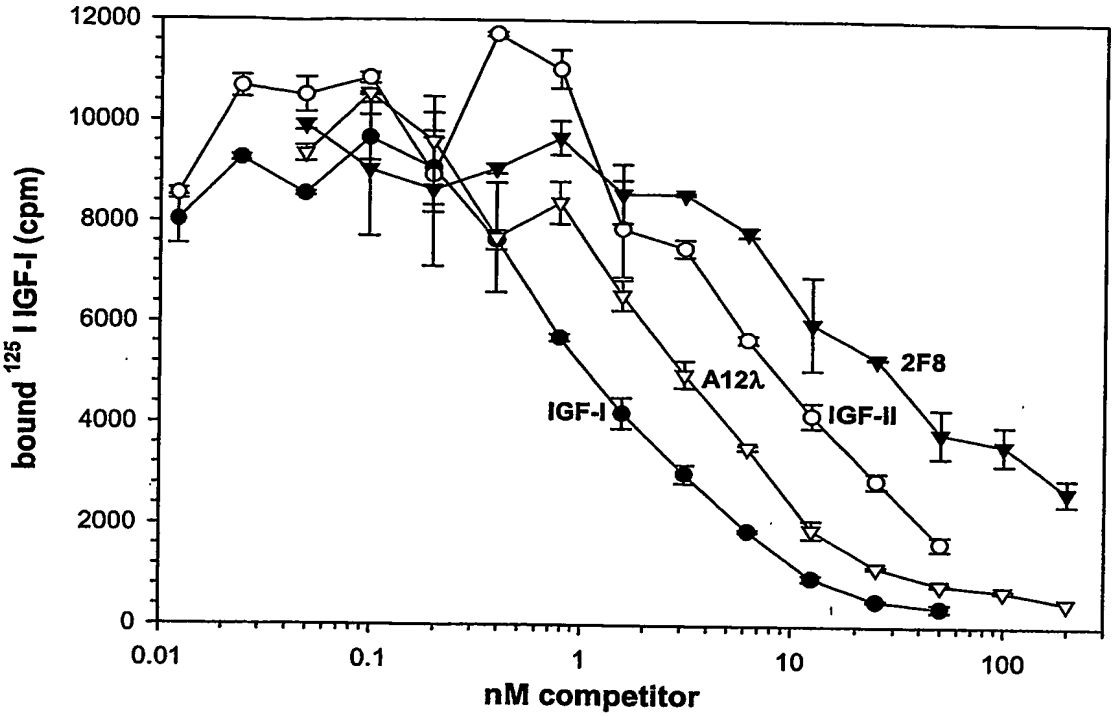

12000
10000
8000
6000
4000
2000
0
bound ^{125}I IGF-I (cpm)
0.01
0.1
1
10
100
nM competitor
2F8
A12λ
IGF-II
IGF-I

Figure 17

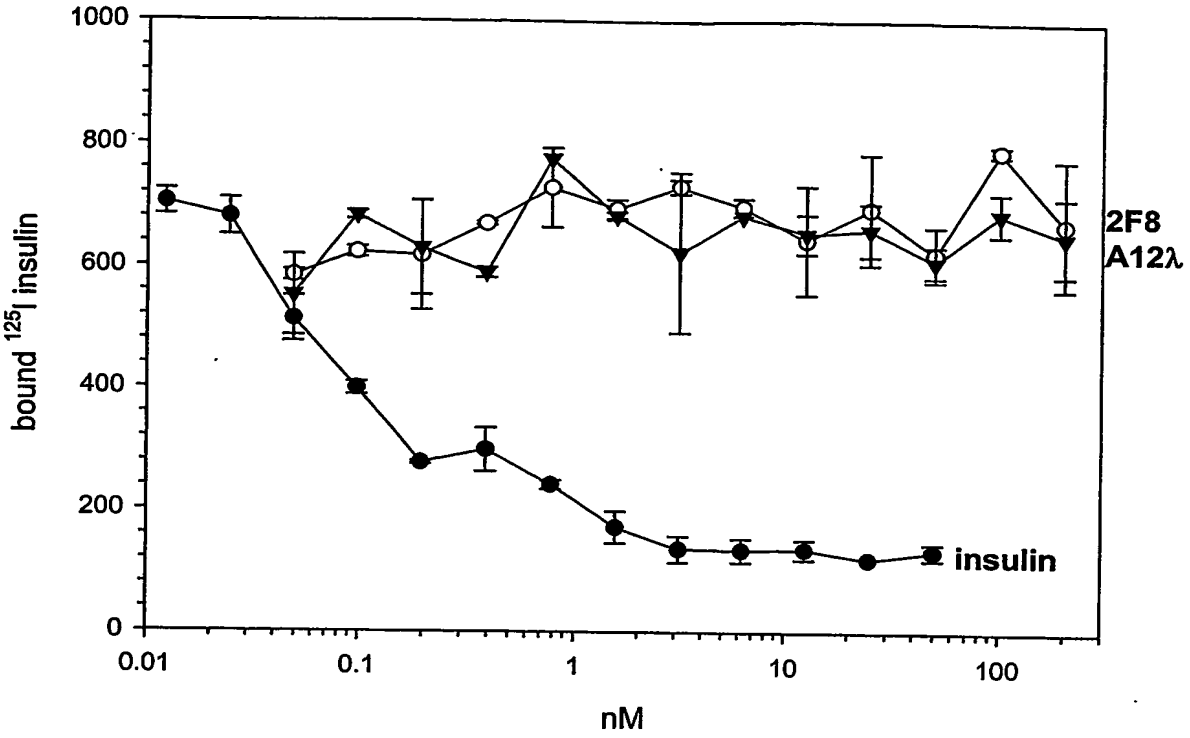

1000
800
600
400
200
0
bound ^{125}I insulin
0.01
0.1
1
10
100
nM
2F8
A12λ
insulin

Figure 18A

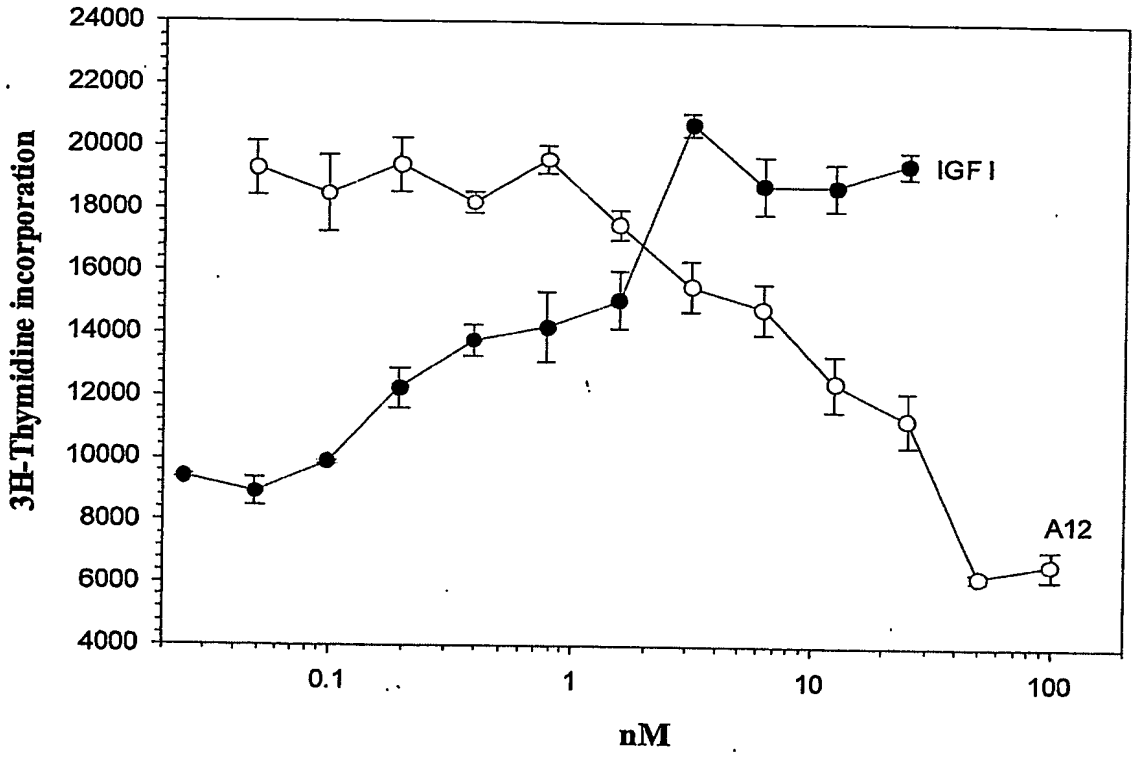

24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
3H-Thymidine incorporation
0.1
1
10
100
nM
IGF I
A12

Figure 18B

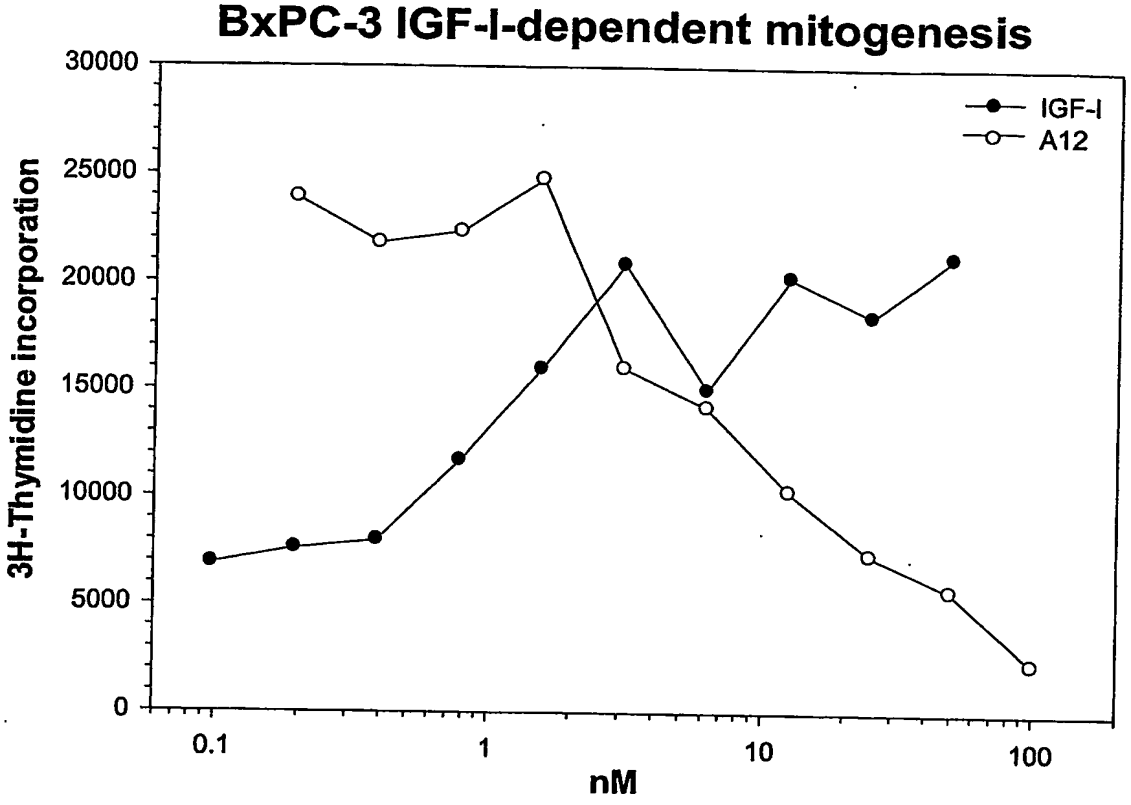

BxPC-3 IGF-I-dependent mitogenesis
3H-Thymidine incorporation
30000
25000
20000
15000
10000
5000
0
0.1
1
10
100
nM
IGF-I
A12

Figure 18C

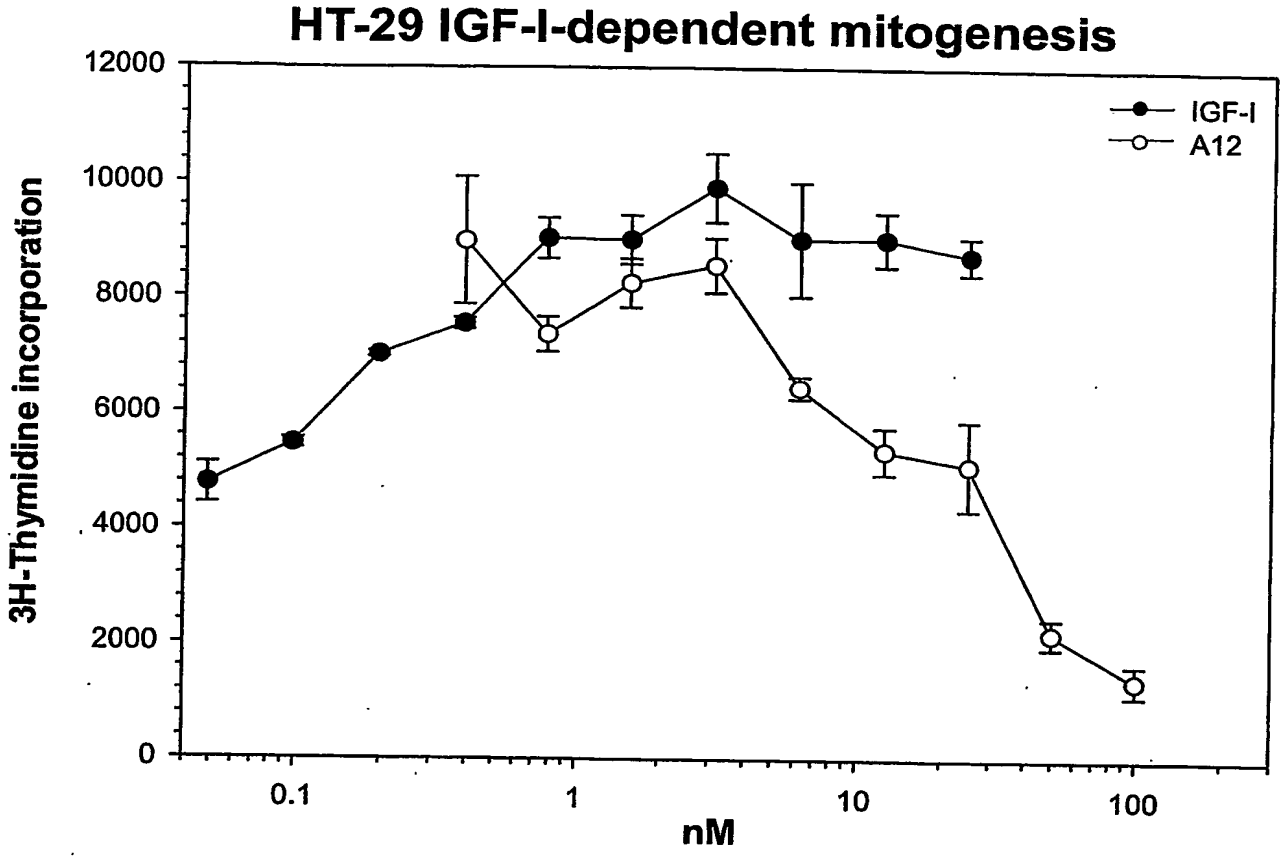

HT-29 IGF-I-dependent mitogenesis
3H-Thymidine incorporation
12000
10000
8000
6000
4000
2000
0
0.1
1
10
100
nM
IGF-I
A12

Figure 19A

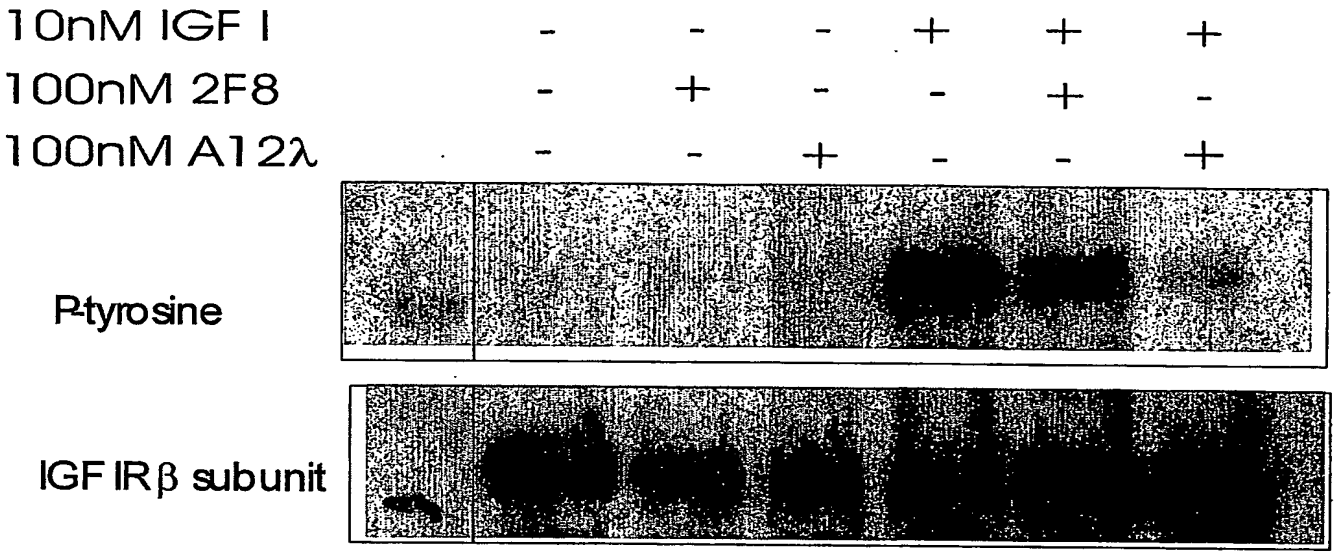


Figure 19B

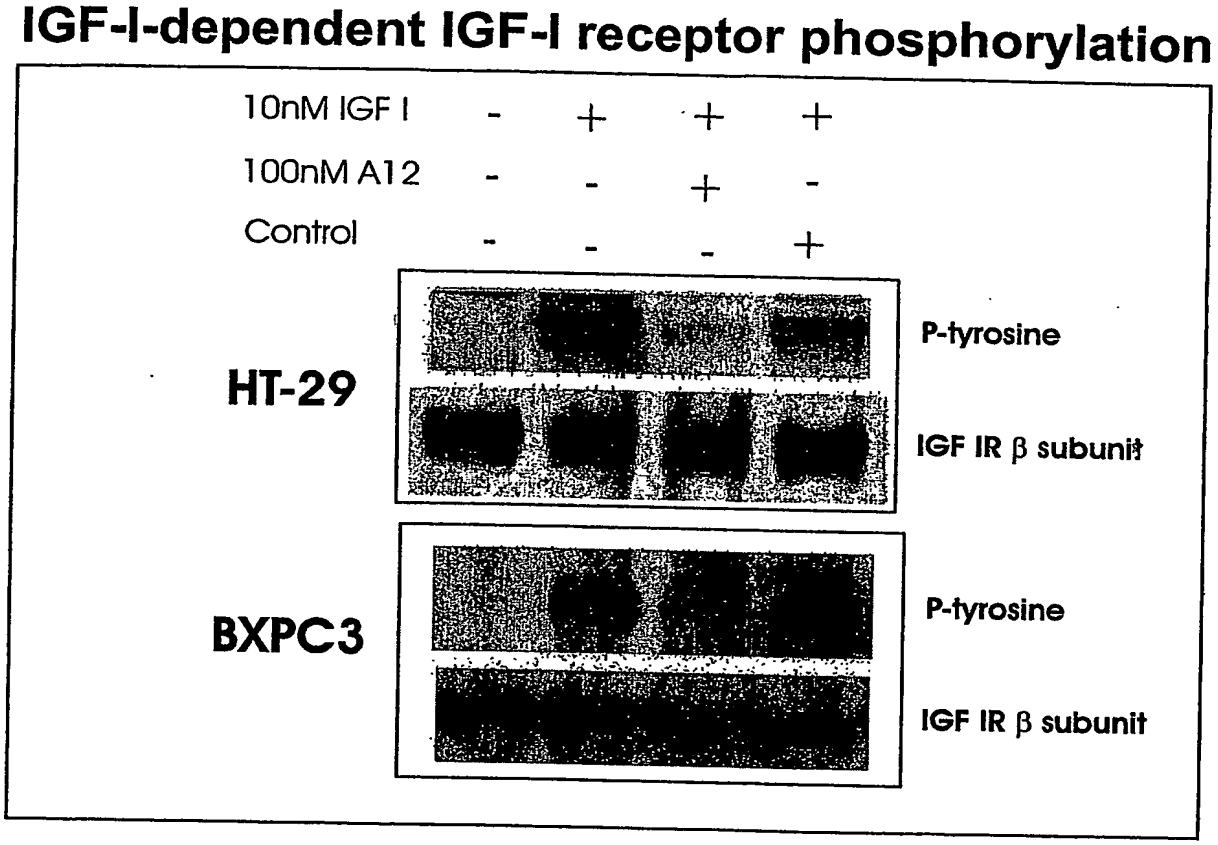
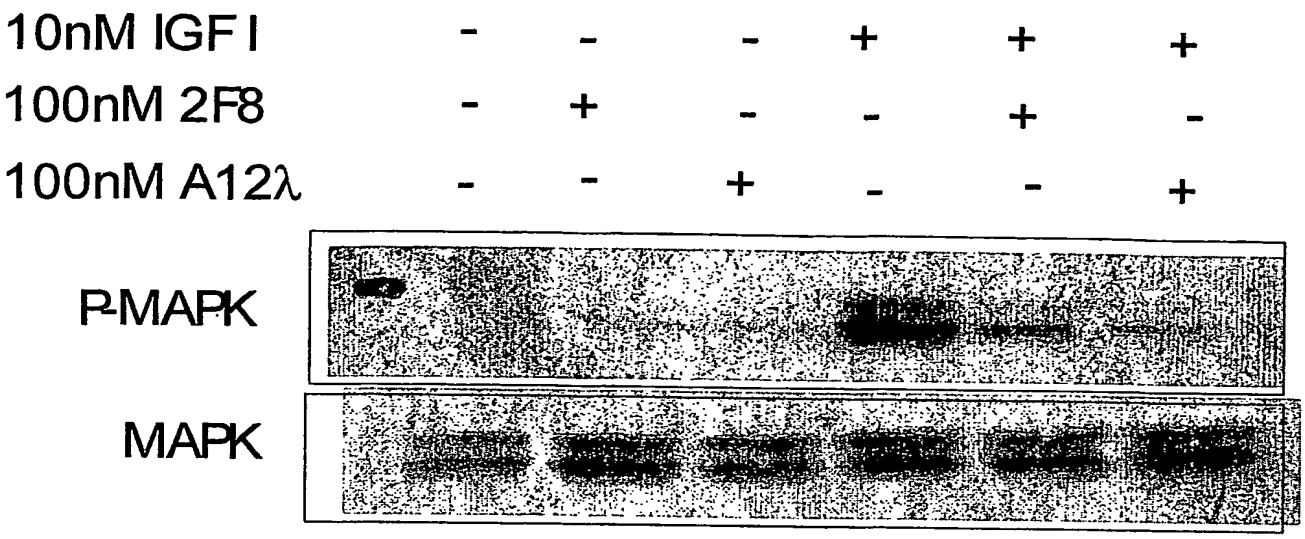

IGF-I-dependent IGF-I receptor phosphorylation
10nM IGF I - + + +
100nM A12 - - + -
Control - - - +
HT-29
P-tyrosine
IGF IR β subunit
BXPC3
P-tyrosine
IGF IR β subunit

Figure 20A



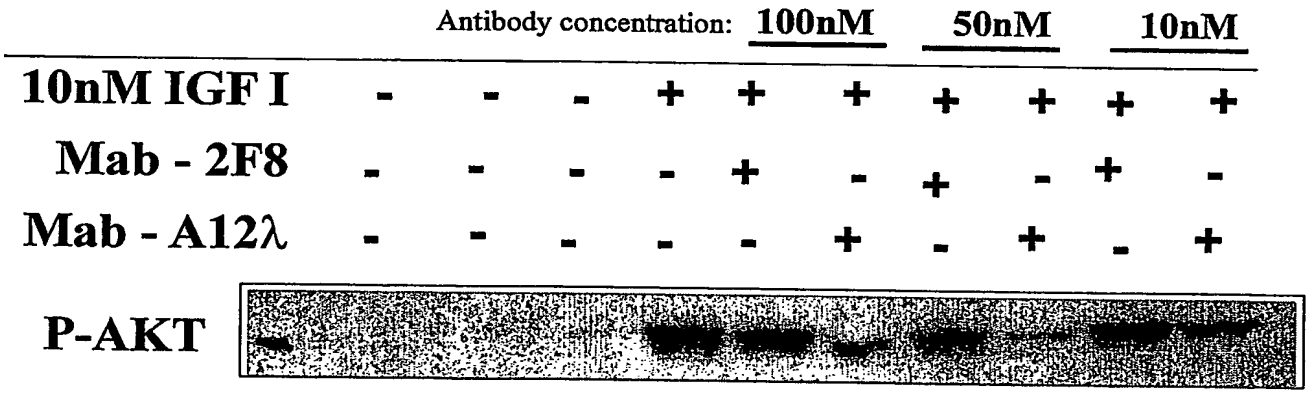


Figure 20B

Figure 21

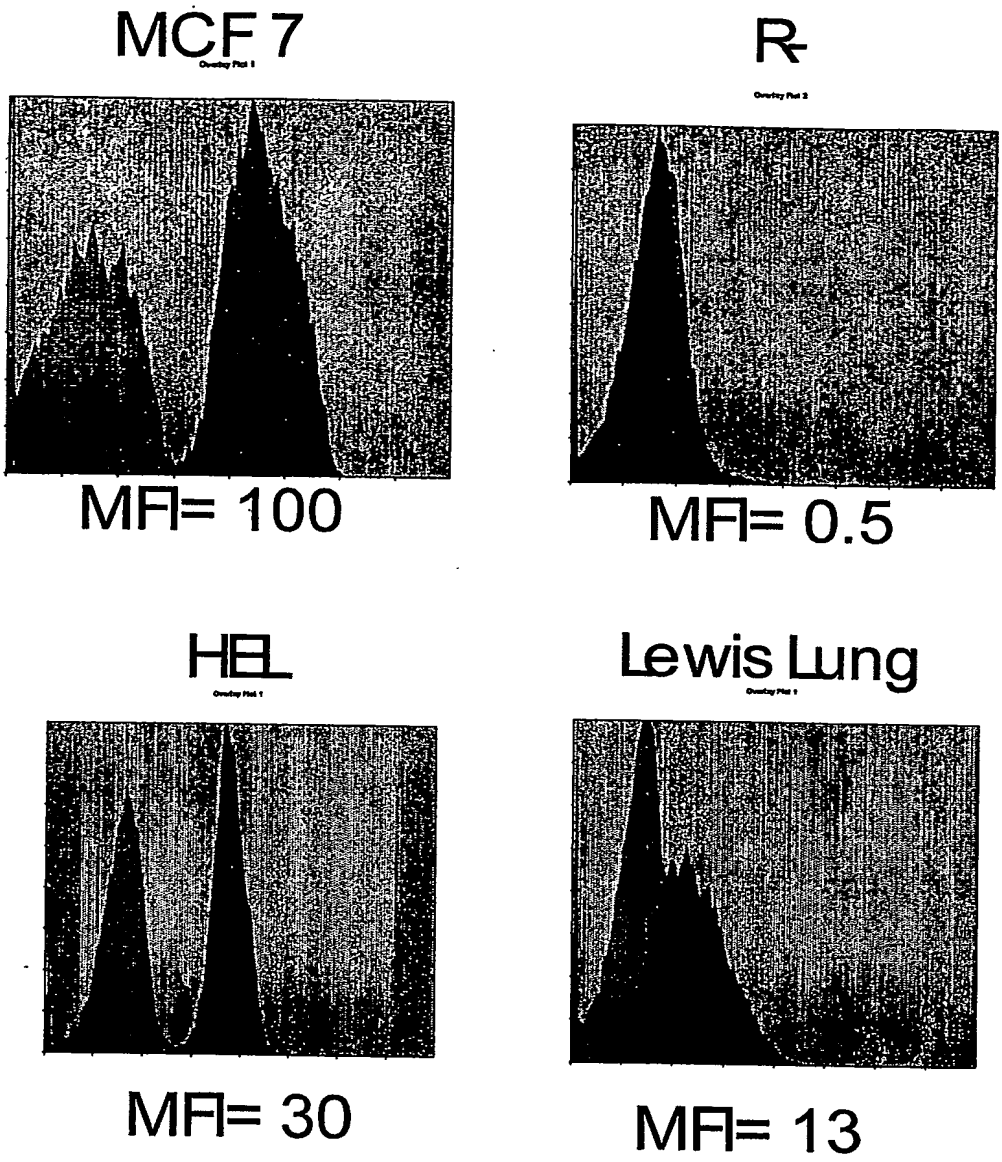


Figure 22A

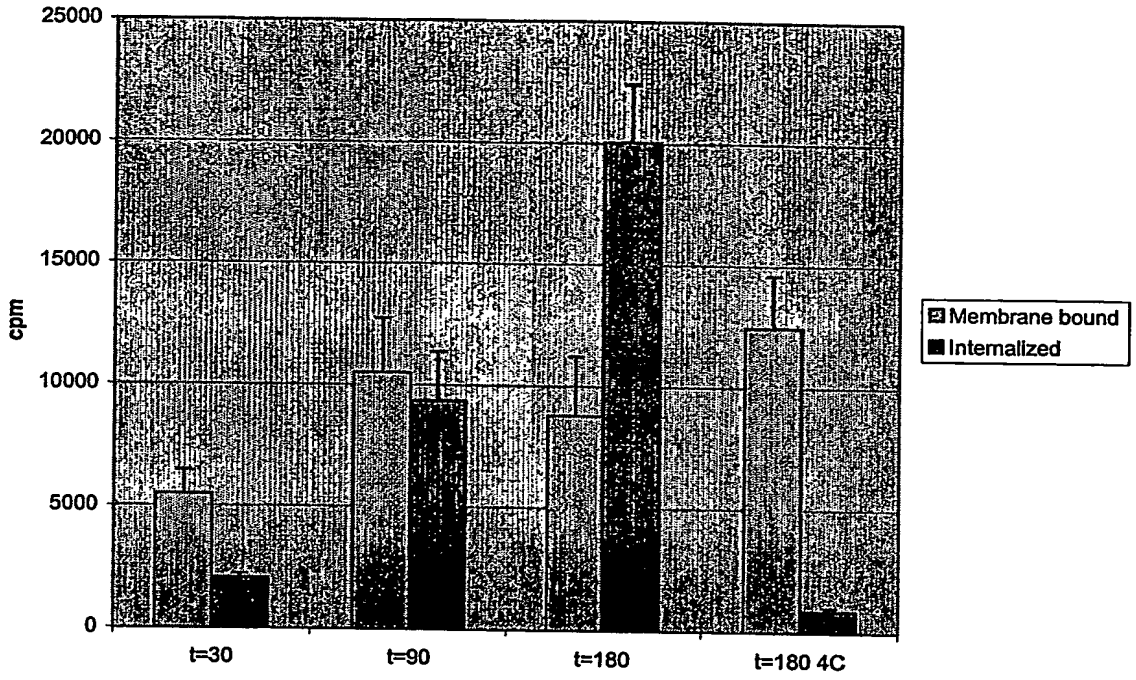

25000
20000
15000
10000
5000
0
cpm
t=30
t=90
t=180
t=180 4C
Membrane bound
Internalized

Figure 22B

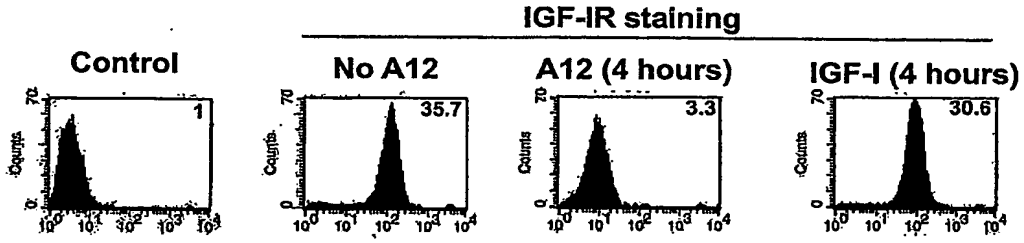

IGF-IR staining
Control
No A12
A12 (4 hours)
IGF-I (4 hours)
1
35.7
3.3
30.6
Counts

Figure 22C

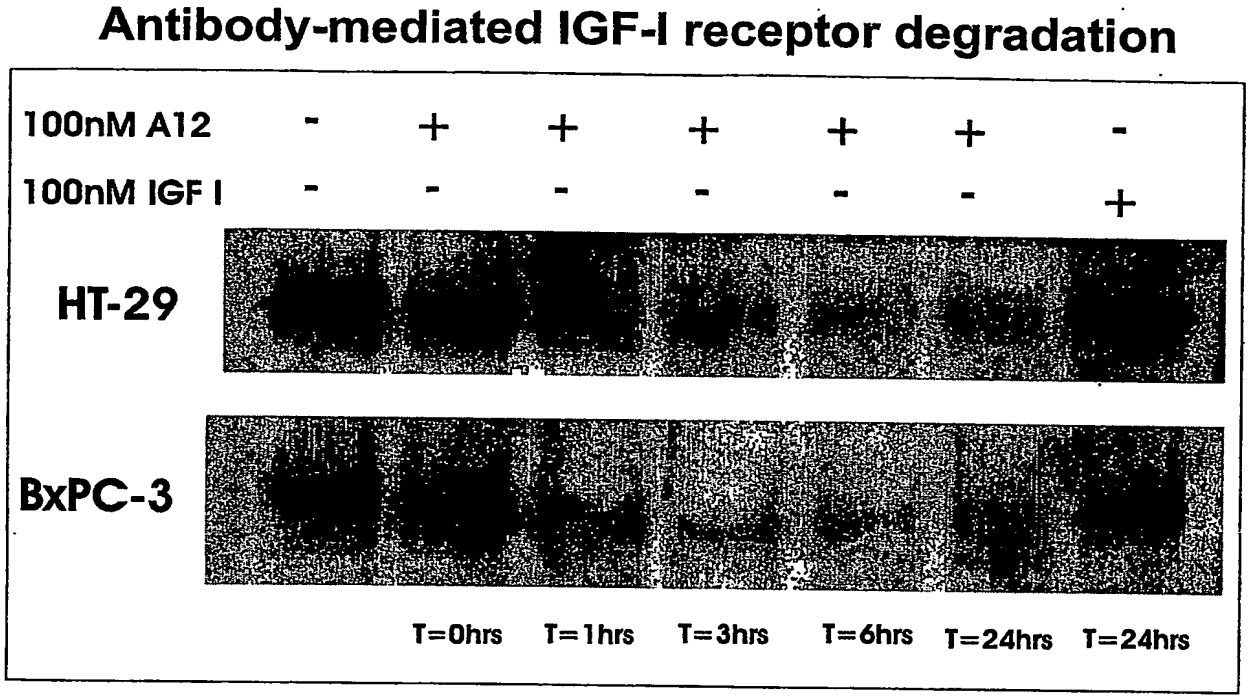

Antibody-mediated IGF-I receptor degradation
100nM A12 - + + + + + -
100nM IGF I - - - - - - +
HT-29
BxPC-3
T=0hrs T=1hrs T=3hrs T=6hrs T=24hrs T=24hrs

Figure 23

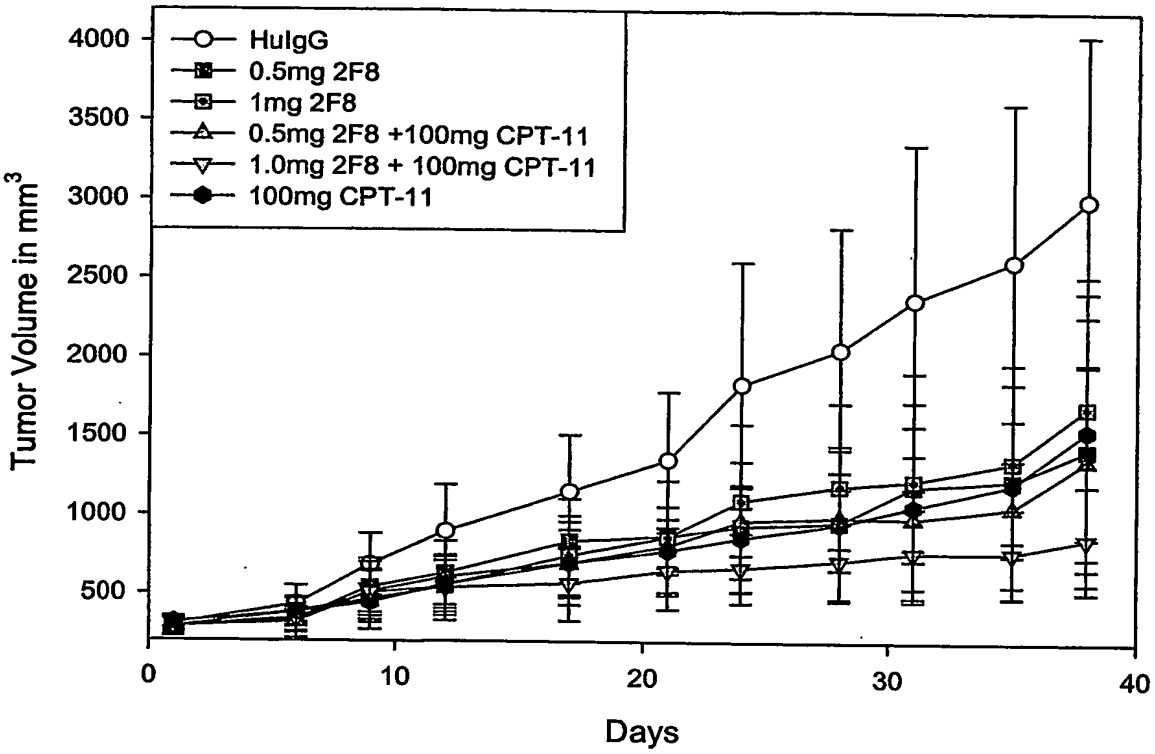

HuIgG
0.5mg 2F8
1mg 2F8
0.5mg 2F8 +100mg CPT-11
1.0mg 2F8 + 100mg CPT-11
100mg CPT-11
Tumor Volume in mm3
4000
3500
3000
2500
2000
1500
1000
500
0
10
20
30
40
Days

Figure 24

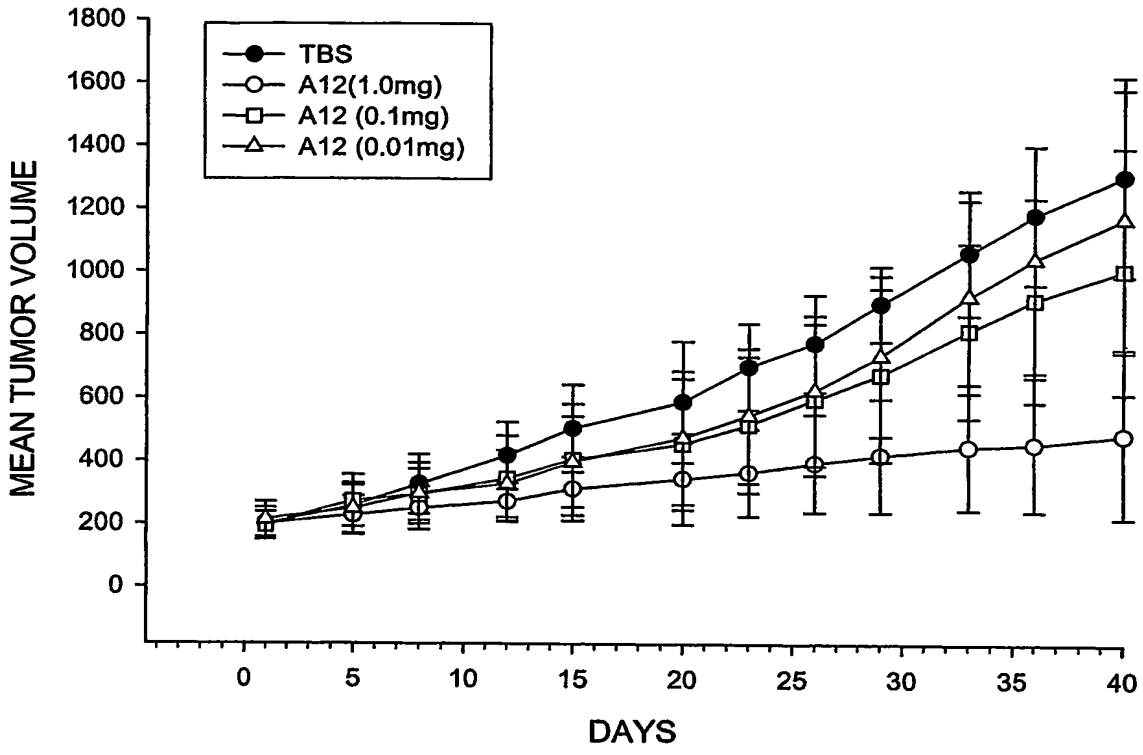

TBS
A12(1.0mg)
A12 (0.1mg)
A12 (0.01mg)
MEAN TUMOR VOLUME
1800
1600
1400
1200
1000
800
600
400
200
0
0
5
10
15
20
25
30
35
40
DAYS

Figure 25

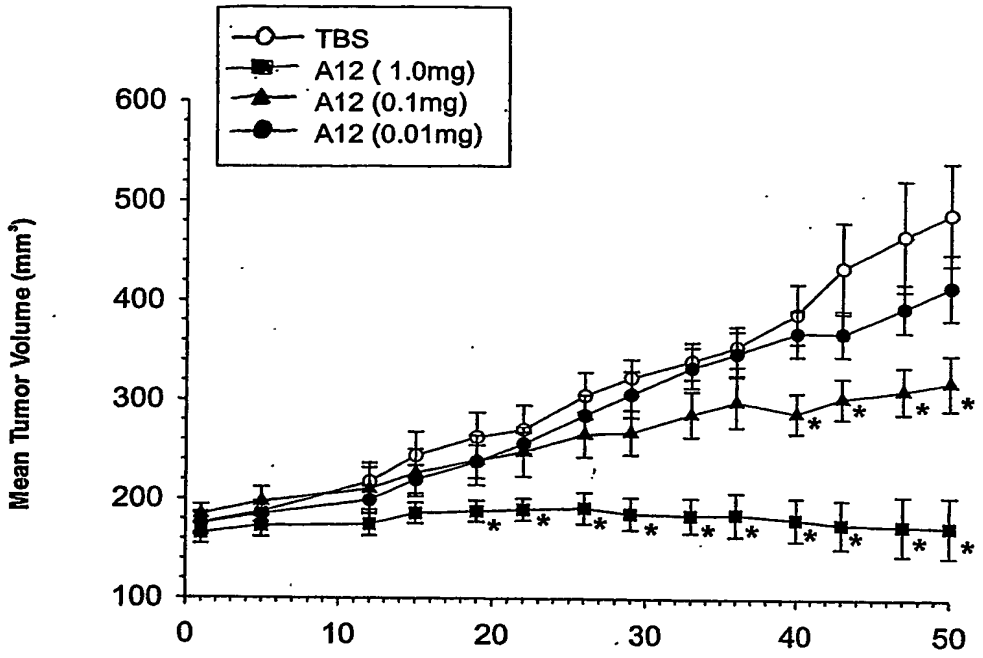

TBS
A12 (1.0mg)
A12 (0.1mg)
A12 (0.01mg)
Mean Tumor Volume (mm³)
600
500
400
300
200
100
0
10
20
30
40
50

Figure 26

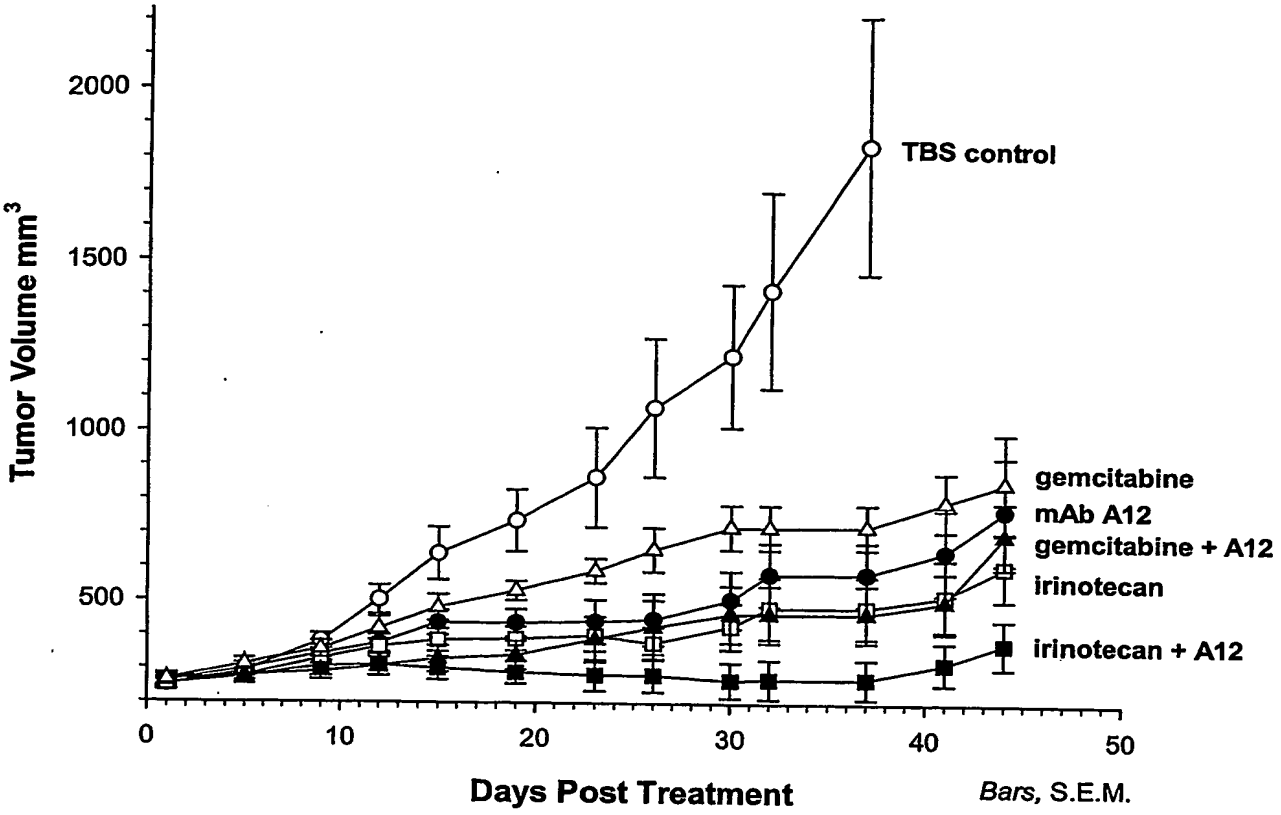
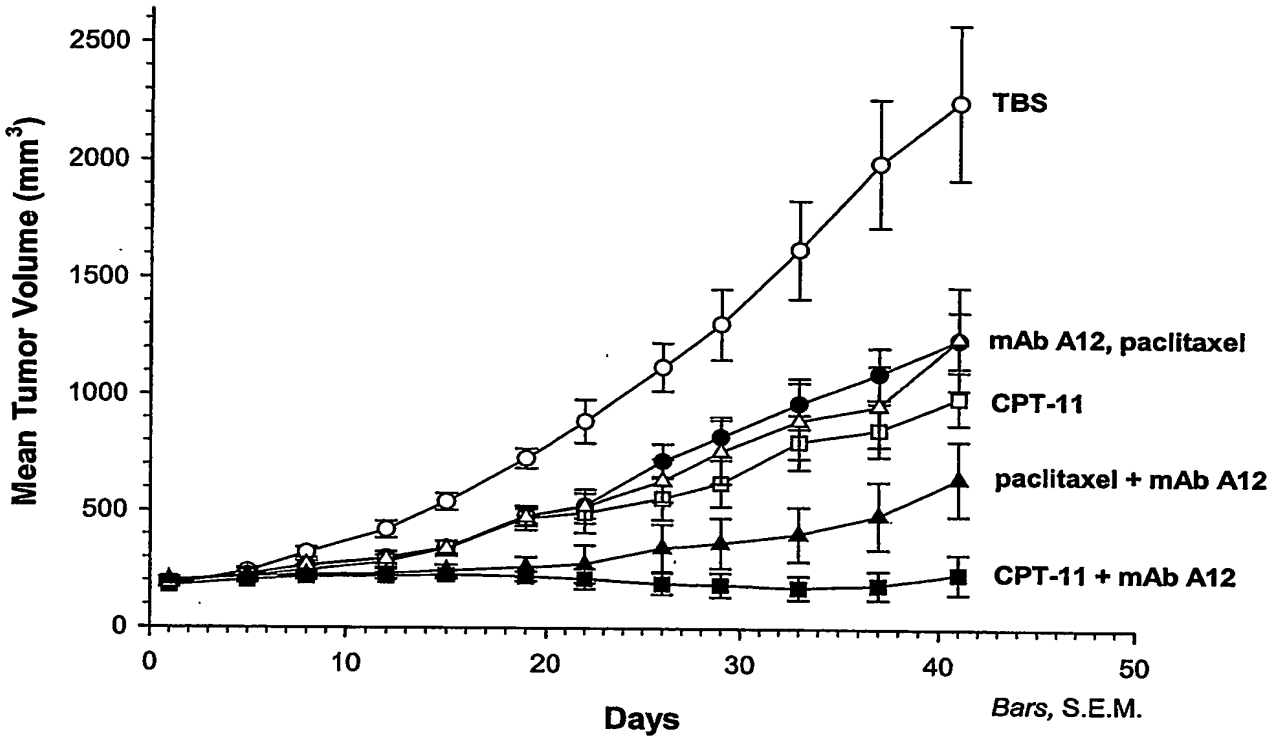

2000
1500
1000
500
Tumor Volume mm3
0
10
20
30
40
50
Days Post Treatment
TBS control
gemcitabine
mAb A12
gemcitabine + A12
irinotecan
irinotecan + A12
Bars, S.E.M.

Figure 27


Mean Tumor Volume (mm3)
2500
2000
1500
1000
500
0
0
10
20
30
40
50
Days
TBS
mAb A12, paclitaxel
CPT-11
paclitaxel + mAb A12
CPT-11 + mAb A12
Bars, S.E.M.